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AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Jacques DUMAS et al.	:	
Serial No.: 09/776,935	:	Group Art Unit: 1617
Filed: December 22, 1998	:	Examiner: WILLIAMS, Leonard M.

For: INHIBITION OF p38 KINASE USING ARYL AND HETEROARYL SUBSTITUTED HETEROCYCLIC UREAS

APPEAL BRIEF

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on October 3, 2006, please consider the following.

The attached check includes the fee as set forth under § 41.20(b)(2).

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

REAL PARTY IN INTEREST

The real party in interest is Bayer Pharmaceuticals Corporation.

RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

STATUS OF CLAIMS

Claims 17-24, 26, and 30-32 are pending in the present application.

Claims 1-16, 25, and 27-29 were cancelled.

Claims 17-24, 26, and 30-32 were rejected.

Claims 17-24, 26, and 30-32 are on appeal.

STATUS OF AMENDMENTS

No amendments were filed after final.

SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention claimed in independent claim 17 is directed to a method for the treatment of rheumatoid arthritis by administering a compound of formula (I). See page 2, lines 11-14; page 7, lines 4-5; and page 8, line 4 to page 15, line 16.

Appellants' invention claimed in independent claim 30 is directed to a method for the treatment of Crohn's disease, rheumatoid arthritis, osteoarthritis, osteroporosis, asthma, septic shock, inflammatory bowel disease, or the result of host-versus-graft reactions by administering a compound of formula (I). See page 2, line 11 to page 5, line 2; page 7, line 4 to page 8, line 2; and page 8, line 4 to page 15, line 16.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejections are:

(1) the rejections under 35 U.S.C. § 112, first paragraph, i.e., whether claims 17-19, 22, 26 and 30-32 are enabled.

(2) the rejections on the ground of nonstatutory obviousness-type double patenting, i.e., whether claims 17-24, 26 and 30-32 are unpatentable over claims 1-16 of copending application no. 09/947,761.

ARGUMENT

The rejections under 35 U.S.C. § 112, first paragraph

The Office Action dated July 3, 2006 (hereinafter Office Action), rejects claims 17-19, 22, 26 and 30-32 under 35 USC § 112, first paragraph, and alleges a lack of enablement for the treatment of rheumatoid arthritis with the compounds recited in the claims. (The enablement rejection was first made in the Office Action dated December 30, 2005, and was maintained and modified in the Office Action dated July 3, 2006.)

First and foremost, there is no indication that one of ordinary skill in the art would have questioned the effect of the drugs in view of the disclosure and the state of the art. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005). Thus, the enablement rejection is improper.

The specification teaches that "inhibition of p38 has been shown to inhibit both cytokine production (eg., TNFα, IL-1, IL-6, IL-8) and proteolytic enzyme production (eg.,

MMP-1, MMP-3) *in vitro* and/or *in vivo*." See page 2 of the specification. Applicants also cite a large volume of prior art that provides the nexus between, for example, TNFα and various diseases, including rheumatoid arthritis. See pages 2-5 of the specification. Applicants teach on page 5 of the specification that "because inhibition of p38 leads to inhibition of TNFα production, p38 inhibitors will be useful in treatment of the above listed diseases," which includes rheumatoid arthritis.

Appellants bring to the attention of the Board of Appeals that there are currently at least three FDA approved rheumatoid arthritis therapeutics whose target is TNFα, e.g., Remicade® (infliximab) of Centocor Inc.; Enbrel® (etanercept) of Immunex/Wyeth; and Humira® (adalimumab) of Abbott, and that there are others being studied and/or in clinical trials, including some p38 MAPK inhibitors.

Appellants additionally provided various abstracts from PubMed with the Reply filed on March 27, 2006, which provide insight into the treatment of rheumatoid arthritis and its relation, i.e., nexus, to p38. For example, see Badger, A.M. et al. (1996) Pharmacological profile of SB 203580, a selective inhibitor of cytokine suppressive binding protein/p38 kinase, in animal models of arthritis, bone resorption, endotoxin shock and immune function. J Pharmacol Exp Ther 279, 1453-1461, which reference predates the current application, and found that SB 203580 is a selective cytokine suppressive binding protein/p38 kinase inhibitor, and that it possesses therapeutic activity in collagen-induced arthritis. The remaining references attached, postdate the application, but provide further support on the art-recognized relation of the inhibition of p38 and the treatment of rheumatoid arthritis. See, for example, Jackson, J.R. et al. (1998) Pharmacological effects of SB 220025, a selective inhibitor of P38 mitogen-activated protein kinase, in angiogenesis and chronic inflammatory disease models. J Pharmacol Exp Ther 284, 687-692; Badger, A.M. et al. (2000) Disease-modifying activity of SB 242235, a selective inhibitor of p38 mitogen-activated protein kinase, in rat adjuvant-induced arthritis. Arthritis Rheum 43, 175-183; Wadsworth, S.A. et al. (1999) RWJ 67657, a potent, orally active inhibitor of p38 mitogen-activated protein kinase. J Pharmacol Exp Ther 291, 680-687; McLay, L.M. et al. (2001) The discovery of RPR 200765A, a p38 MAP kinase inhibitor displaying a good oral anti-arthritic efficacy. Bioorg Med Chem 9, 537-554; Kumar S et al. (2001) IL-1- and TNF-induced bone resorption is mediated by p38 mitogen activated protein kinase. J Cell Physiol. 187, 294-303; Suzuki M et al (2000) The role of p38 mitogen-activated protein kinase in IL-6 and IL-8 production from the TNF-alpha- or IL-1beta-stimulated rheumatoid synovial fibroblasts. FEBS Lett. 465, 23-7.

Thus, a nexus between the activity of the compounds and the claimed methods is more than adequately established in the specification and is more than adequately recognized by those of ordinary skill in the art. Thus, a person of ordinary skill in the art would not question the usefulness of a compound that inhibits p38 to treat rheumatoid arthritis.

Additionally, the Office Action admits that the specification provides a showing that specific compounds of the invention are effective at inhibiting p38. This is more than sufficient under the law to demonstrate the compound will treat rheumatic arthritis.

As such there is no basis for the enablement rejection.

Nevertheless, the Office Action maintained the enablement rejection and in response alleges that "there is no indication that inhibition of p38 invariably inhibits each of the cytokines listed ..., nor is there any indication that the inhibition of p38 would invariably lead to the treatment of rheumatoid arthritis. ... doesn't mean that any inhibition of TNFα would treat rheumatoid arthritis." (Emphasis added.) See the paragraph spanning pages 7 and 8 of the Office Action. (Applicants note, as a side issue, that the claims do not require that p38 inhibit each of the cytokines listed, nor is treatment "invariably" claimed. The independent claims, for example, do not limit the treatment by any mechanism.) The Office Action also alleges that "none [of the compounds] are shown to be actually effective at treating rheumatoid arthritis." (Emphasis added.) See the paragraph with the heading "Working Examples" on page 7 of the Office Action.

There is no evidence cited in the Office Action to support of any of the above allegations, e.g., evidence that supports the allegation that not every inhibitor of p38 will treat rheumatoid arthritis is lacking. Thus, the allegations are bare allegations.

Moreover, the medical arts are not full of invariable treatments, and the law does not require them to be either. For example, even the treatment of the common cold with well established commercial medications does not lead to the invariable treatment of all patients.

Also, it is not necessary for the claimed invention to provide "invariable" treatment to satisfy the requirement of 35 U.S.C. § 112, first and second paragraph. See, for example, *Atlas Powder Company v. E.I. Du Pont De Nemours & Company*, 224 USPQ 409 (CAFC 1984), *In re Dinh-Nguyen and Stenhagen*, 181 USPQ 46 (CCPA, 1974), *In re Geerdes*, 180 USPQ 789 (CCPA, 1974), *Ex parte Janin*, 209 USPQ 761 (POBA 1980). A claim may encompass inoperable subject matter, i.e., "it is not a function of the claims to exclude all inoperative embodiments."

In addition, neither indications of invariable treatments or actual treatments are required to be demonstrated in a patent application to enable an invention directed to a

method of treatment of a disease. Instead, The Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1441 (Fed. Cir. 1995), stated that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Applicants also point to *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure only established the basic pharmacology for the compounds, but where no examples were provided. The specification stated that the compounds of the invention possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

With respect to the adequacy of the showing, laboratory data provided is more than adequate to satisfy the statute. Such data is the art-accepted marker of potential treatments, and is adequate for patentability. In *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985), the Federal Circuit stated that

> in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

The Office Action on page 3 alleges that it is not clear whether the p38 IC_{50} range of 1nM to 10 μM applies to all exemplified compounds or only to compounds in Table 1. Table 1 lists all the exemplified compounds. Thus, there is no lack of clarity issue.

The Office Action also alleges that the range provided for the results of the tested compounds is not adequate for the understanding of the scope and breadth of the invention since it does not teach the activity profile of the tested compounds. Appellants respectfully disagree. The scope of the claimed invention is clearly recited in the claims. As for the tested compounds, appellants teach that all the compounds tested have activity in the claimed range. This is more than what is required. There is no requirement of any tests or examples

or any disclosure of activity profiles. See, for example, Marzocchi, supra, stating that "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The Office Action at various places alleges that the breadth of the claims regarding the number of compounds "exacerbates the nature of the invention." Appellants respectfully disagree. The specification, even though not necessary for an enabling disclosure, provides 38 species of the claimed genus, which is admitted in the Office Action. There is no requirement that an applicant provide examples directed to the preparation and/or testing of each and every species of a claimed invention. See, for example, In re Angstadt, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art"); Utter v Higara, 845 F.2d at 998-99, 6 USPQ2d 1714 (CAFC 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses).

The Office Action raises the issues of possible "side effects," "serious toxicity," "drug-drug interactions" and "significant adverse consequences." Applicants submit that these are safety issues which have nothing to do with whether the claimed method, satisfies the requirement of 35 U.S.C. § 112. Side effects, serious toxicity, drug-drug interactions, and significant adverse consequences are safety issues, which are independent of whether the compounds exhibit the activity claimed. These safety issues are left up to the Food and Drug Administration and not to the Patent and Trademark Office. The courts have repeatedly noted that the patent and drug-approval processes are distinct. See, for example, *In re Watson*, 186 USPQ 11 (CCPA 1975), *Scott v. Finney*, 32 USPQ2d 1115 (CA FC 1994), *In re Jolles*, 206 USPQ 885 (CCPA 1980), and *In re Anthony*, 162 USPQ 594 (CCPA 1969).

The Office Action also alleges that "one of ordinary skill in the art would be forced to perform an exhaustive search for the embodiments ... suitable to practice the claimed invention." See Office Action page 9, last paragraph. Applicants respectfully disagree. The compounds of this invention have been clearly defined and methods for determining their activity have been provided in the specification and are known in the art. Determining the activity of the compounds in the claims is not undue experimentation in the field of pharmaceuticals, but rather an industry wide acceptable routine amount of testing. As discussed in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988), the "test is not merely quantitative,

since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Applicants provide specific guidance as to how the claimed compounds can be tested for activity levels and actually provide data for specific compounds. Additionally, those of ordinary skill in the art, as supported by the vast amount of prior art in this area, know how to proceed in view of the disclosure. While the amount of work may require considerable effort (although not admitted), no undue experimentation is required.

For all the foregoing reasons, reversal of the rejection is respectfully requested.

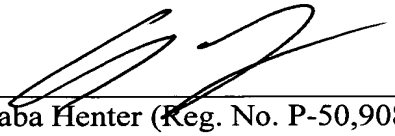
The rejections on the ground of nonstatutory obviousness-type double patenting

The claims of the present application are rejected as allegedly unpatentable over claims 1-16 of 09/947,761. The Office Action, with respect to the compounds of the methods claimed, alleges that both the current application's claims and of '761 define A and B as having equivalent scope and breadth. This allegation is incorrect.

There is not even a single point of overlap between the A and/or B groups of the claims of '761 and of the present application. For example, the current application's independent claims define A as a heteroaryl selected from the group of three specific 5-membered heteroaryl groups which each have specific subsituents, including each having an R^2 substituent, which is defined as a C_6-C_{14} aryl or substituted C_6-C_{14} aryl. There is no such corresponding C_6-C_{14} aryl or substituted C_6-C_{14} aryl substituent on either group A or B of '761, nor is one suggested by the claims. Also, the B group of the present claims is selected from a list of specific cyclic and/or aromatic groups, each substituted by –Y-Ar. Neither group A or B of '761 claims or even suggests a corresponding substituent –Y-Ar. Thus, in sum, both A and B of the present claims differ from and do not overlap the A and B groups of the '691 application. Additionally, such modifications of the groups A and B of '761 that one of ordinary skill in the art would be motivated to prepare compounds of the present method claims are not taught or suggested by the claims of '761.

Thus, the obviousness-type double patenting rejection should be reversed and is courteously requested.

Respectfully submitted,



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Attorney Docket No.: Bayer-12-P1

Date: December 4, 2006

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CLAIMS APPENDIX

17. A method for the treatment of rheumatoid arthritis which comprises administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof

I

wherein B is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl substituted by -Y-Ar; and is optionally substituted by one or more substitutents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-3 and each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, phenyl, pyridinyl, naphthyl, isoquinolinyl, quinolinyl, up to per halo-substituted C_1-C_{10} alkyl, up to per halo-substituted C_2-C_{10} alkenyl, up to per halo-substituted C_1-C_{10} alkoxy, up to per halo-substituted C_3-C_{10} cycloalkyl, and

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_2-C_{10} alkenyl and up to per-halosubstituted C_3-C_{10} cycloalkyl,

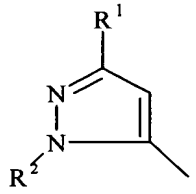
wherein Y is - O-, -S-, $-N(R^5)-$, $-(CH_2)-_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-NR^5C(O)NR^5\ NR^{5'}-$, $-NR^5C(O)-$, $-C(O)NR^5-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^5)-$, $-O(CH_2)_m-$, $-CHX^a$, $-CX^a{}_2-$, $-S-(CH_2)_m-$ and $-N(R^5)(CH_2)_m-$,

m = 1-3, and X^a is halogen; and

Ar is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl, optionally substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and

each Z is independently selected from the group consisting of –CN, =O, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)-NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-C(O)R^5$, $-NR^5C(O)R^{5'}$, $-SO_2R^5$, $SO_2NR^5R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxyl, C_3-C_{10} cycloalkyl, up to per halo-substituted C_1-C_{10} alkyl, and up to per halo-substituted C_3-C_{10} cycloalkyl, and

wherein A is a heteroaryl selected from the group consisting of



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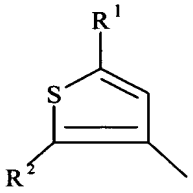
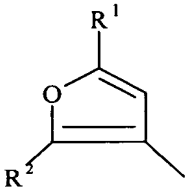


and


wherein R^1 is selected from the group consisting of C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl,

wherein R^2 is C_6-C_{14} aryl, or substituted C_6-C_{14} aryl,

wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

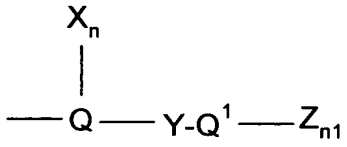
wherein n = 0-3 and each V is independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-C(O)R^5$, $-OC(O)NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-SO_2R^5$, $-SOR^5$, $-NR^5C(O)R^{5'}$, $-NO_2$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

where V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^5$, $-NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and $-NO_2$,

wherein R^5 and R^6 are each independently as defined above.

18. A method as in claim 17 wherein R^2 is phenyl or substituted phenyl.

19. A method of claim 17, wherein B is



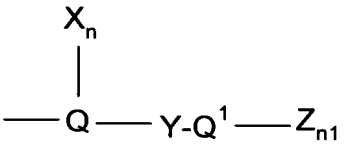
wherein

Y is as defined in claim 17,

Q and Q^1 are independently selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, optionally substituted by halogen, up to per-halo substitution, Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, and C_3-C_6-cycloalkyl wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution, and

n and n1 are, each independently 0-3.

20. A method as in claim 17, wherein B is



wherein

Q is phenyl,

Q^1 is phenyl or pyridinyl,

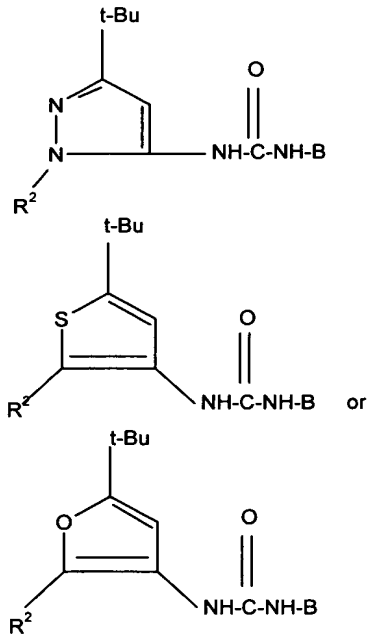
Y is -O-, -S- or $-CH_2$,

X and Z are independently CF_3, NO_2 or CN,

n and n1 are, each independently 0-3, and

wherein Q and Q^1 are optionally substituted by one or more Cl and/or F.

21. A method as in claim 17, which comprises administering a compound of one of the formulae or a pharmaceutically acceptable salt thereof:



wherein B and R^2 are as defined in claim 17.

22. A method as in claim 21, wherein R^2 is phenyl or substituted phenyl.

23. A method as in claim 17, comprising administering an amount of compound of formula I effective to inhibit p38.

24. A method as in claim 17, wherein the compound of formula I displays p38 activity (IC_{50}) better than 10μM as determined by an in-vitro kinase assay.

26. A method according to claim 30, wherein R^1 is t-butyl.

30. A method for the treatment of Crohn's disease, rheumatoid arthritis, osteoarthritis, osteroporosis, asthma, septic shock, inflammatory bowel disease, or the result of host-versus-graft reactions which comprises administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof

I

wherein B is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl substituted by -Y-Ar; and is optionally substituted by one or more substitutents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-3 and each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, - SR^5, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, phenyl, pyridinyl, naphthyl, isoquinolinyl, quinolinyl, up to per halo-substituted C_1-C_{10} alkyl, up to per halo-substituted C_2-C_{10} alkenyl, up to per halo-substituted C_1-C_{10} alkoxy, up to per halo-substituted C_3-C_{10} cycloalkyl, and

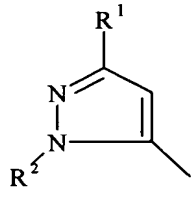
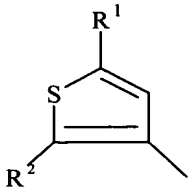
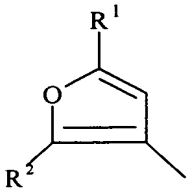
wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_2-C_{10} alkenyl and up to per-halosubstituted C_3-C_{10} cycloalkyl,

wherein Y is - O-, -S-, $-N(R^5)$-, $-(CH_2)$-$_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-NR^5C(O)NR^5$ $NR^{5'}$-, $-NR^5C(O)$-, $-C(O)NR^5$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-O(CH_2)_m$-, $-CHX^a$, $-CX^a_2$-, $-S-(CH_2)_m$- and $-N(R^5)(CH_2)_m$-,

m = 1-3, and X^a is halogen; and

Ar is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl, optionally substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, =O, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, -C(O)- NR^5, $-NO_2$, $-OR^5$, - SR^5, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-C(O)R^5$, $-NR^5C(O)R^{5'}$, $-SO_2R^5$, $SO_2NR^5R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxyl, C_3-C_{10} cycloalkyl, up to per halo-substituted C_1-C_{10} alkyl, and up to per halo-substituted C_3-C_{10} cycloalkyl, and

wherein A is a heteroaryl selected from the group consisting of



and


wherein R^1 is selected from the group consisting of C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl,

wherein R^2 is C_6-C_{14} aryl, or substituted C_6-C_{14} aryl,

wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

wherein n = 0-3 and each V is independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-C(O)R^5$, $-OC(O)NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-SO_2R^5$, $-SOR^5$, $-NR^5C(O)R^{5'}$, $-NO_2$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

where V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^5$, $-NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and $-NO_2$,

wherein R^5 and R^6 are each independently as defined above.

31. A method as in claim 30, wherein R^2 is phenyl.

32. A method as in claim 30, wherein R^2 is a substituted C_6-C_{14} aryl.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None